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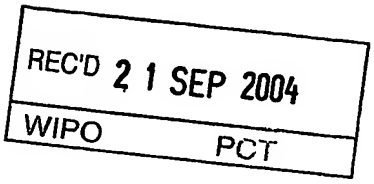

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I also certify that the attached copy of the request for grant of a Patent (Form 1/77) bears a correction, effected by this office, following a request by the applicant and agreed to by the Comptroller-General.

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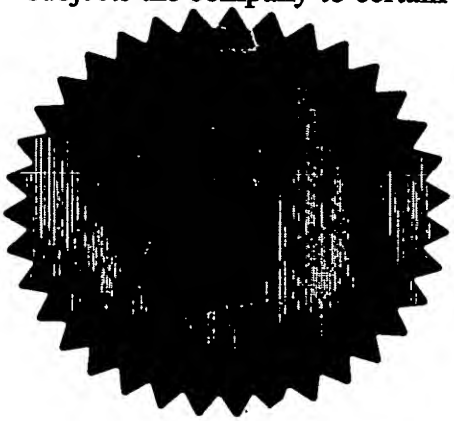

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Signed A W Brewer

Dated 27 July 2004

Patents Form 1/77

[redacted] Act 1977
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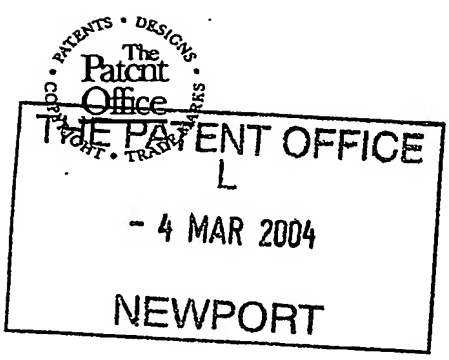
4 MAR 2004



1/77

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

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1. Your reference 101183-2

04MAR04 E878201-1 D02934
P01/7700 0.00-0404859.1 NONE

2. Patent application number *(The Patent Office will fill in this part)* 0404859.1

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

~~AstraZeneca AB~~
~~SE-151 85 Sodertalje~~
~~Sweden~~

AstraZeneca UK Limited
15 Stanhope Gate
London
W1K 1LN

AR 4/77 8.4.04

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation: Sweden

4. Title of the invention

CHEMICAL COMPOUND

5. Name of your agent *(if you have one)*

Kevin BILL

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

AstraZeneca
Global Intellectual Property
P O Box 272
Mereside, Alderley Park
Macclesfield,
Cheshire SK10 4GR

Patents ADP number *(if you know it)* 08179707001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

Patents Form 1/77

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Continuation sheets of this form	
Description	9
Claim(s)	2
Abstract	
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature [signature] Date 3/3/2004

12. Name and daytime telephone number of person to contact in the United Kingdom: Shirley Douglas - 01625 510057

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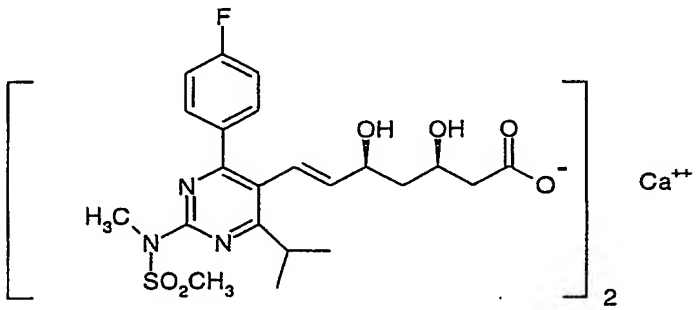
CHEMICAL COMPOUND

The present invention relates to a novel crystalline chemical compound and more particularly to a novel crystalline form of bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt, hereinafter referred to as "the Agent", and illustrated in Formula (I) hereinafter, which compound is an inhibitor of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG CoA reductase) and is useful as a pharmaceutical agent, for example in the treatment of hyperlipidemia, hypercholesterolemia and atherosclerosis, as well as other diseases or conditions in which HMG CoA reductase is implicated. The invention also relates to processes for the manufacture of the crystalline form, pharmaceutical compositions comprising the crystalline form and the use of the crystalline form in medical treatment.



(I)

European Patent Application, Publication No. 521471 (hereinafter EPA 521471), which is herein incorporated by reference, discloses an amorphous (powder) form of the Agent, prepared by dissolving the corresponding sodium salt in water, adding calcium chloride and collecting the resultant precipitate by filtration.

International Patent Application WO 00/42024 discloses a crystalline form of the Agent, referred to as Form A therein, which is prepared from a mixture of water and one or more organic solvents, for example, a 1:1 mixture of acetonitrile and water. However no suitable conditions were found for preparation of Form A from water without the presence of an organic co-solvent. The use of organic solvents in large scale manufacture is generally undesirable for environmental reasons (for example, the disposal of large volumes of waste), and safety reasons (for example, if the product is a pharmaceutical, the need to ensure that organic solvents are removed from the final product). Therefore there is an on-going need to find crystalline forms of the Agent which can be produced from water alone.

We have now surprisingly and unexpectedly discovered that the Agent can be prepared in a second crystalline form from water without the need for an organic co-solvent.

According to the present invention there is provided a crystalline hydrated form of the Agent having an X-ray powder diffraction pattern with peaks at 2-theta (2θ) = 8.8, 13.1 and 21.5° (hereinafter referred to as Form B).

According to the present invention there is provided a crystalline hydrated form of the Agent having an X-ray powder diffraction pattern with peaks at 2-theta (2θ) = 4.3, 8.8, 13.1, 13.7, 21.5, 22.8 and 28.9°.

According to the present invention there is provided a crystalline hydrated form of the Agent having an X-ray powder diffraction pattern with peaks at 2-theta (2θ) = 4.3, 8.8, 13.1, 13.7, 15.2, 15.8, 17.5, 21.5, 21.9, 22.8, 24.5 and 28.9°.

According to the present invention there is provided a crystalline hydrated form of the Agent having an X-ray powder diffraction pattern substantially as shown in Figure 1.

Forms B obtained according to the present invention is substantially free from other crystal and non-crystal forms of the Agent. The term "substantially free from other crystal and non-crystal forms" shall be understood to mean that the desired crystal form contains less than 50%, preferably less than 20%, more preferably less than 10%, more preferably less than 5% of any other forms of the Agent.

The X-ray powder diffraction (referred to herein as XRPD or XRD) spectra was determined by mounting a sample of the crystalline form on Siemans single silicon crystal (SSC) wafer mounts and spreading out the sample into a thin layer with the aid of a microscope slide. Using a Siemens D5000 diffractometer, the sample was spun at 30 revolutions per minute (to improve counting statistics) and irradiated with X-rays generated by a copper long-fine focus tube operated at 40kV and 40mA with a wavelength of 1.5406 angstroms. The collimated x-ray source was passed through an automatic variable divergence slit set at V20 (20mm path length) and the reflected radiation directed through a 2mm antiscatter slit and a 0.2mm detector slit. The sample was exposed for 4 seconds per 0.02 degree 2-theta increment (continuous scan mode) over the range 2 degrees to 40 degrees 2-theta in theta-theta mode. The running time was 2 hours 6 minutes and 40 seconds. The instrument was equipped with a scintillation counter as detector. Control and data capture was by means of a DECpc LPv 433sx personal computer running with Diffrac AT (Socabim) software.

The X-ray powder diffraction spectra of a typical sample of Form B is shown in Figure 1 hereinafter.

It will be understood that the 2-theta values of the X-ray powder diffraction pattern may vary slightly from one machine to another or from one sample of Form B to another, and so the values quoted are not to be construed as absolute. It will also be understood that the relative intensities of peaks may vary according to the orientation of the sample under test so that the intensities shown in the XRD trace included herein are illustrative and not intended to be used for absolute comparison.

Typically Form B is obtained in a hydrated form with, for example, a water content of about 9-10% w/w, for example about 9% w/w.

Form B may be crystallised from a saturated solution of the Agent in aqueous [(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] sodium salt (hereinafter referred to as 'Sodium Salt'). Suitably the amorphous form of the Agent is used as starting material and may be obtained, for example, as described in EPA 521471. The sodium salt may be prepared by treatment of the methylamine salt of the Agent with sodium hydroxide as described in WO 00/49014 and in Example 1 hereinafter.

Therefore in a further aspect of the present invention is provided a process for the manufacture of a crystalline hydrated form of a compound of formula (I) which comprises forming crystals from a saturated solution of compound of formula (I) in aqueous bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] sodium salt.

A further aspect of the present invention provides a process for the manufacture of a crystalline hydrated form of a compound of formula (I) which comprises forming crystals from a saturated solution of the amorphous form of the compound of formula (I) in aqueous bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino] pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] sodium salt.

Saturation of the sodium salt solution with the Agent means addition of, for example the amorphous form to the Sodium Salt solution until the solution is saturated. Further amorphous form is added to maintain the saturation once crystallisation of Form B has started.

The process of the invention is conveniently carried out between 20 and 45°C, more conveniently between 30 and 45°C, even more conveniently between 37 and 43°C, and preferably at about 40°C.

Form B may also be formed by seeding an aqueous solution or slurry of the amorphous form of the Agent, or by prolonged stirring of a solution of the amorphous form.

The utility of the compound of the invention may be demonstrated by standard tests and clinical studies, including those described in EPA 521471.

According to a further feature of the invention is a method of treating a disease condition wherein inhibition of HMG CoA reductase is beneficial which comprises administering to a warm-blooded mammal an effective amount of Form B of the Agent. The invention also relates to the use of Form B in the manufacture of a medicament for use in a disease condition.

The compound of the invention may be administered to a warm-blooded animal, particularly a human, in need thereof for treatment of a disease in which HMG CoA reductase is implicated, in the form of a conventional pharmaceutical composition. Therefore in another aspect of the invention, there is provided a pharmaceutical composition comprising Form B in admixture with a pharmaceutically acceptable carrier.

Such compositions may be administered in standard manner for the disease condition that it is desired to treat, for example by oral, topical, parenteral, buccal, nasal, vaginal or rectal administration or by inhalation. For these purposes the Agent may be formulated by means known in the art into the form of, for example, tablets, capsules, aqueous or oily solutions, suspensions, emulsions, creams, ointments, gels, nasal sprays, suppositories, finely divided powders or aerosols for inhalation, and for parenteral use (including intravenous, intramuscular or infusion) sterile aqueous or oily solution or suspensions or sterile emulsions. A preferred route of administration is oral. The Agent will be administered to humans at a daily dose in, for example, the ranges set out in EPA 521471. The daily doses may be given in divided doses as necessary, the precise amount of the Agent received and the route of administration depending on the weight, age and sex of the patient being treated and on the particular disease condition being treated according to principles known in the art.

According to a further feature of the invention, there is provided a process for the manufacture of a pharmaceutical composition containing Form B as active ingredient, which comprises admixing Form B together with a pharmaceutically acceptable carrier.

Under certain circumstances the Agent may exist in a crystalline form related to Form B which generally possesses long-range order, but only limited short-range order, and which generally has a lower water content than Form B. This form, related to Form B is hereinafter referred to as Form B-1. An XRD trace of Form B-1 is shown in Example 2.

Form B-1 is produced by the removal of water from the crystal lattice of Form B. Upon dehydration, the long-range structure of Form B is retained in Form B-1, but Form B-1 has only limited short-range order. Form B-1 may be formed by heating a sample of Form B to 60 °C or by storing a sample of Form B at 0 % Relative Humidity (RH) using equipment such as a DVS (Dynamic Vapour Sorption) instrument, for example a Surface Measurement Systems DVS_1, as described in Example 2. Form B-1 may be converted back to Form B by appropriate exposure to water, for example by slurrying in water. As illustrated in Example 2, Form B-1 demonstrates a distinct XRD pattern in comparison to that of Form B. The XRD pattern of Form B-1 may be determined by the method hereinbefore described for Form B.

Therefore in another aspect there is provided a 'dehydrated hydrate' form of the Agent having an X-ray powder diffraction pattern with peaks at 2-theta (2θ) = 4.4, 7.7, 9.0 and 20.7 at 0 % RH. In a further aspect there is provided a 'dehydrated hydrate' of the Agent having an X-ray powder diffraction pattern with peaks at 2-theta (2θ) = 4.4, 9.0 and 20.7 at 0 % RH.

Exposure of Form B-1 to humidities above 0% RH allows water to re-enter the crystal lattice to a level dictated by the RH of the environment. However, water vapour does not easily reorder the structure to reproduce Form B, hence the material continues to lack short-range order and water is easily lost on lowering the relative humidity. The absorption and desorption of water may lead to small shifts in the XRPD peaks.

The invention will now be illustrated by the following Examples.

Example 1

Aqueous sodium hydroxide (8% w/w, 27.2 ml) was added to a stirred mixture of [(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] methylamine salt (30 g) in purified water (234 ml) at 20°C and the mixture was stirred for 15 min. The mixture may be filtered if necessary to remove insoluble material. The mixture was concentrated under reduced pressure at <40°C until 142 ml of distillate collected. Water (90 ml) was added and the mixture again concentrated under reduced pressure at <40°C until 90ml of distillate collected. The resulting solution of [(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] sodium salt was made up to a volume of 295 ml with water (125 ml) at 40°C and bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid]

calcium salt (8g) was added. After stirring for approximately 20 hours a gel was observed. After a further 7 hours of stirring at 40°C crystallisation was observed (confirmed by optical microscopy). Further bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt (amorphous, 17g) and water (100ml) were added. The thick slurry was stirred for a further 16 hours at 40°C after which time the material appeared totally crystalline by optical microscopy. The crystalline material was cooled to 20°C, isolated, washed with water (3 x 90 ml) and dried under vaccuum at approximately 35°C.

X-ray powder diffraction (XRD):

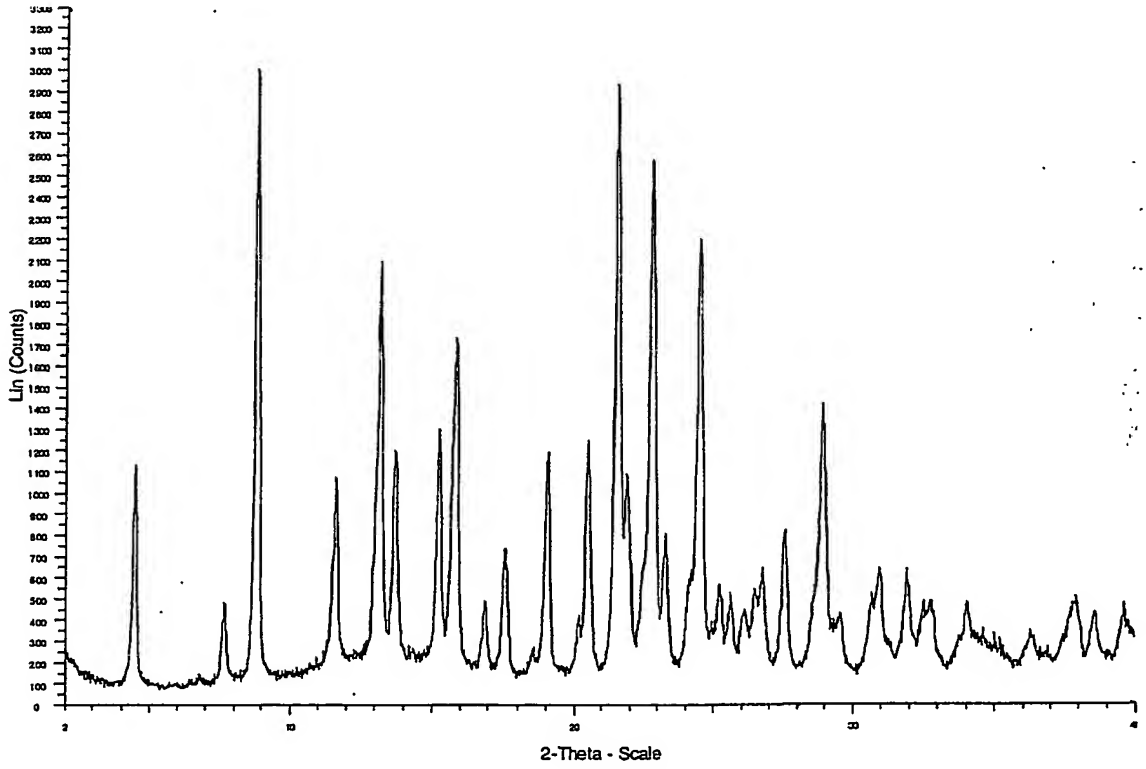


Figure 1

Peak Number	2θ	d-Spacing	Relative Intensity (>20%)
1	4.3	20.2	37.5
2	8.8	10.1	100
3	13.1	6.7	69.5
4	13.7	6.5	39.9
5	15.2	5.8	43.1
6	15.8	5.6	57.5
7	17.5	5.1	24.3
8	21.5	4.1	97.6
9	21.9	4.1	36.0
10	22.8	3.9	85.6
11	24.5	3.6	73.1
12	28.9	3.1	47.1

Water content 9.1% w/w

^{1}H NMR (400 MHz, DMSO-D6) δ ppm: 1.2 (d, 3H) 1.2 (d, 3H) 1.3 (m, 1H) 1.5 (m, 1H) 2.0 (dd, 1H) 2.1 (dd, 1H) 3.4 (s, 3H) 3.5 (s, 3H) 3.8 (m, 1H) 4.2 (q, 1H) 5.5 (dd, 5.4 Hz, 1H) 6.5 (dd, 1H) 7.3 (m, 2H) 7.7 (m, 2H)

Example 2

A sample of Form B (approximately 6 mg) was dispensed into a glass sample pan and suspended from the balance of an SMS Dynamic Vapour Sorption (DVS) instrument. The DVS instrument was then used to hold at 0 %RH, 30 °C, overnight (after this time period the change in sample mass was < 0.002%/min over at least an hour). The sample was then analysed immediately by XRD. The sample was exposed for 0.40 sec per 0.0357° 2θ over the range 3° to 30° 2θ in continuous scan, theta-theta mode.

The following trace (Figure 2) is an example XRD trace of a sample of Form B-1 which has been stored at 0 % RH. It will be appreciated that variations in the water content of the

sample of Form B-1 will cause variations in the precise 2θ values described below, such variations in water content resulting for example by the conditions of storage of Form B-1.

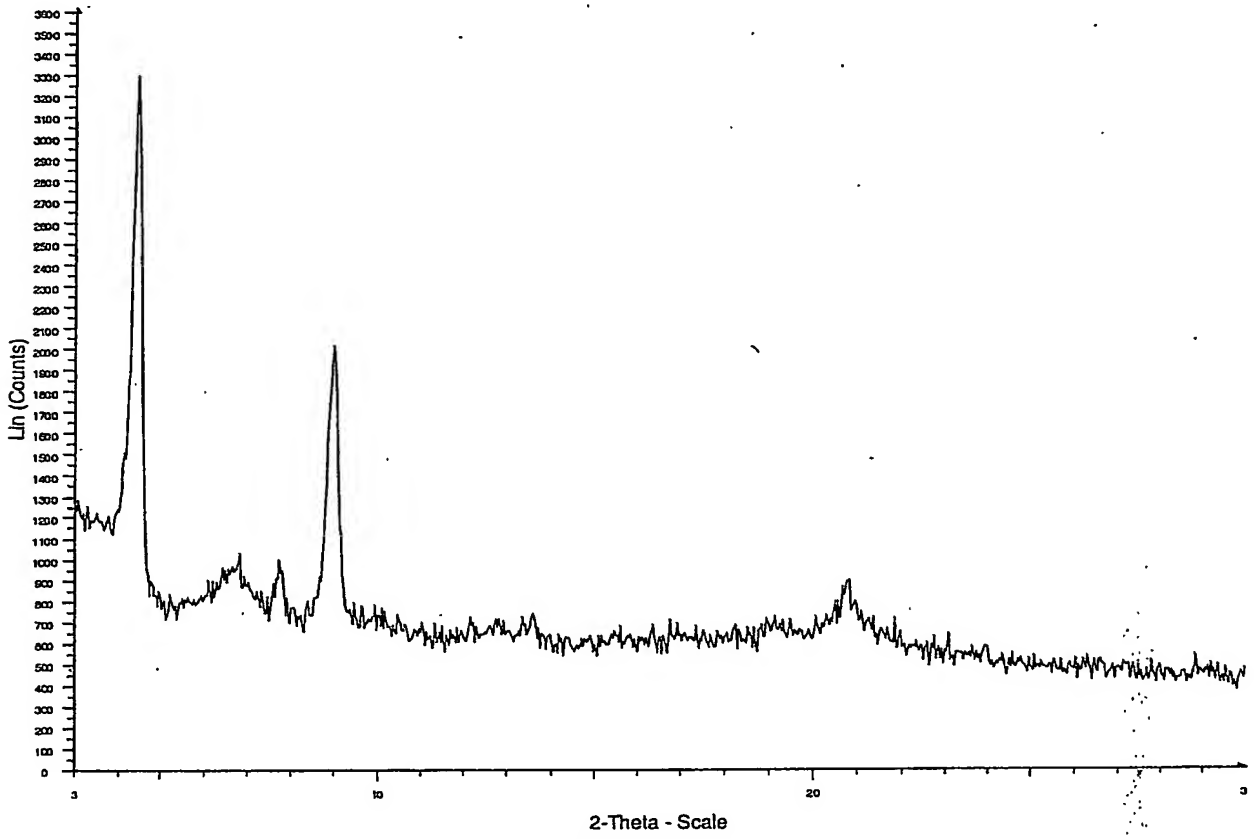


Figure 2

Peak Number	2θ	d-Spacing	Relative Intensity
1	4.4	20.0	100
2	7.7	11.4	26
3	9.0	9.9	58
4	20.7	4.3	22

The following figure (Figure 3) is a comparison of Forms B and B-1:

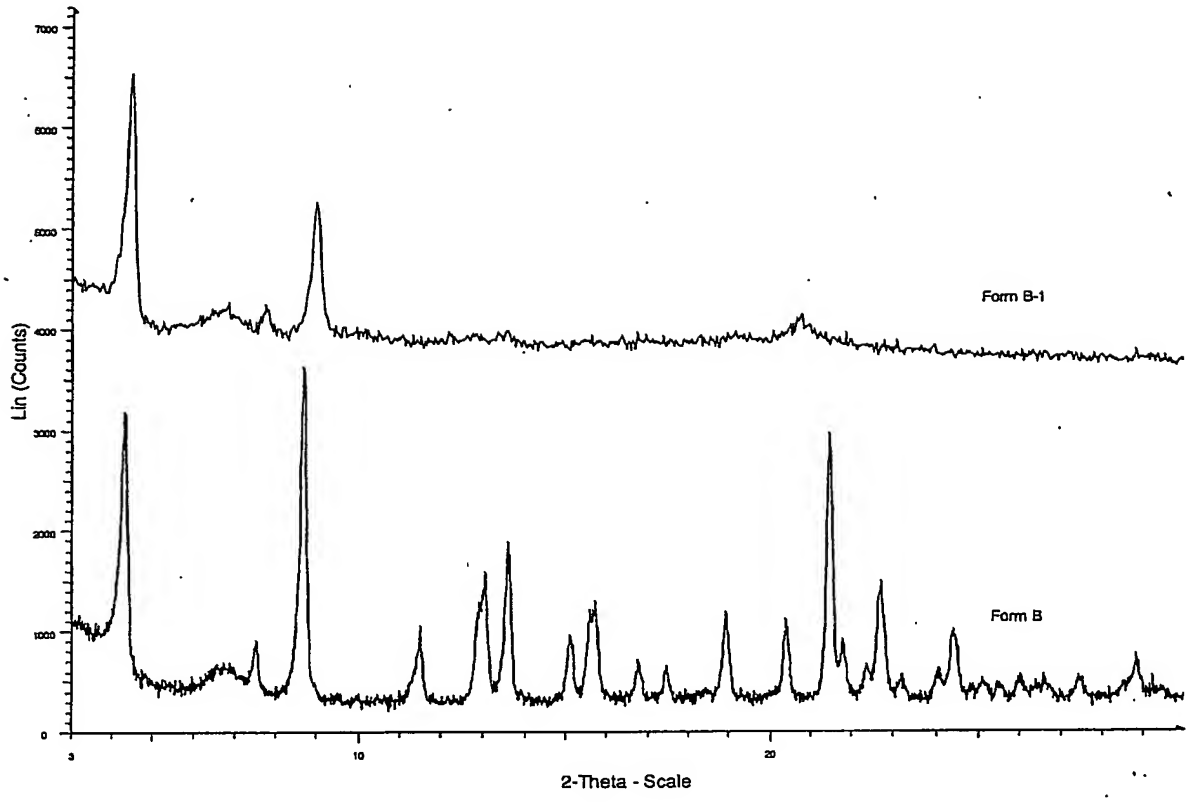
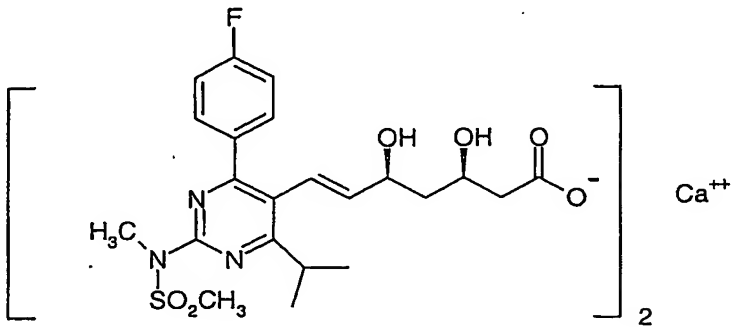

Form B-1
Form B
Lin (Counts)
2-Theta - Scale
0
1000
2000
3000
4000
5000
6000
7000
3
10
20

Figure 3

Claims

1. A crystalline hydrated form of the compound bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt of the formula I



I

having an X-ray powder diffraction pattern with peaks at 2-theta (2θ) = 8.8, 13.1 and 21.5°.

2. A crystalline form as claimed in Claim 1 with an X-ray powder diffraction pattern with peaks at 2-theta (2θ) = 4.3, 8.8, 13.1, 13.7, 21.5, 22.8 and 28.9°.

3. A crystalline form as claimed in Claim 1 with an X-ray powder diffraction pattern with peaks at 2-theta (2θ) = 4.3, 8.8, 13.1, 13.7, 15.2, 15.8, 17.5, 21.5, 21.9, 22.8, 24.5 and 28.9°.

4. A crystalline form as claimed in Claim 1, Claim 2 or Claim 3 which contains about 9-10% water.

5. A pharmaceutical composition comprising a crystalline form as claimed in any one of the preceding claims, together with a pharmaceutically acceptable carrier.

6. A process for the manufacture of a crystalline form as claimed in claim 1 which comprises forming crystals from a saturated solution of compound of formula I in aqueous bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] sodium salt.

7. A process for the manufacture of a pharmaceutical composition as claimed in claim 5 which comprises admixing a crystalline form as claimed in claim 1 together with a pharmaceutically acceptable carrier.

8. The use of a crystalline form as claimed in claim 1 in the manufacture of a medicament.

9. A method of treating a disease condition wherein inhibition of HMG CoA reductase is beneficial which comprises administering to a warm-blooded mammal an effective amount of a crystalline form as claimed in claim 1.